REVIEW ARTICLE

Regulatory requirements for medical devices in different Asian countries (India, China, and Japan)

Yadala Sruthi, M. Naga Pavithra, D. Prasanthi

Department of Regulatory Affairs, G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India

Abstract

Since the use of medical devices is increasing globally, the market for them has recently begun to grow. For the diagnosis and management of diseases, millions of patients rely on medical devices. The way that medical devices are regulated differs from nation to country and is determined by each regulatory body. Medical devices are controlled by the Pharmaceuticals and Medical Devices Agency and Ministry of Health, Labour and Welfare in JAPAN, the National Medical Product Administration in China, and the Central Drug Standard Control Organization in India. The laws of these nations, the International Medical Device Regulators Forum, and the Medical Device Product Working Group were examined. Benefits of harmonising rules are also discussed. Medical devices are thought to be a blessing for the health-care system because they are life-saving instruments. Nevertheless, these devices have a number of negative side effects in addition to their therapeutic benefits. To manage such negative impacts, a cohort vigilance system that worked well was required. Material vigilance had been introduced as a result of this. A materiovigilance is an investigation and monitoring events that come about as a result of using medical equipment. It handles more than just adverse events but also to bring for international harmony, focusing on these goals, the guiding ideas, viewpoints, and methods. In addition, the instances that have already occurred suggest that ongoing monitoring of medical equipment in use is necessary to safeguard patients' health. The existing guidelines for medical device regulation and the post-market vigilance framework were looked at and addressed.

Key words: Medical devices, Regulations, International Medical Device Regulators Forum, Asian medical device regulations

INTRODUCTION

Drugs and medical devices are both utilized all around the world. It is necessary to harmonize national standards due to the rapidly expanding worldwide market for medical devices to reduce regulatory obstacles, promote commerce, and increase access to innovative technologies. In addition, for local businesses and governments, harmonization lowers the cost of putting rules into effect. The governments of Australia, Canada, Japan, the European Union, and the United States of America established the global harmonization task force (GHTF) in 1993 to solve these challenges. The GHTF's mission is to promote regulatory methods and standards that are consistent with medical device safety, effectiveness, and quality. The GHTF also encourages technological advancement and makes international trade easier. Harmonized guidance materials for fundamental regulatory procedures are published and disseminated as the main strategy used to achieve its objectives. These documents, which were created by four different GHTF Study Groups, can then be adopted or put into practice by national regulatory organizations that are members or by others. Members of the technical committee include those from national medical device regulatory agencies and the regulated industry. The following harmonized definition for medical devices has been suggested by the GHTF.[1]

The term "medical device" refers to any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or

Address for correspondence:
Dr. D. Prasanthi, Department of Pharmaceutics,
G. Pulla Reddy College of Pharmacy, Mehdipatnam,
Hyderabad, Telangana, India. Mobile: +91-9490052147.
E-mail: prasanthidhanu@gmail.com

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calibrator, software, material, or other comparable or related item that is intended to be used by humans, either alone or in combination, for one or more of the following specific purposes: Diagnosis, prevention, monitoring, treatment, or alleviation of disease; diagnosis, monitoring, relief from pain from an injury; or investigative purposes,[2] providing data for medical use through *in vitro* examination of human body specimens that does not achieve its primary intended action in or on the human body by pharmacological, immunological, or metabolic means but may be aided in its function by such methods.[1]

PHASES OF A MEDICAL DEVICE'S LIFE CYCLE

The key stages of a medical device's life cycle are from conception, development to disposal. To make the regulatory system simpler to understand, the activity phases have been condensed. For instance, the development phase involves clinical trials, prototype testing, design verification/validation, and development planning. The phases listed below may overlap and interact in real life.

It is crucial to understand that a medical device's performance and safety can be impacted by any of these stages. The following are some instances of how each phase can result in health risks:

1. Conceptualization and creation
2. Production
3. Labeling and packaging
4. Promotion
5. Purchase
6. Utilization
7. Disposal.[1]

MATERIOVIGILANCE

The use of medical equipment has dramatically increased. As a result, it is essential to guarantee their effectiveness and quality. However, there are differences in device quality, and even the best gadget could malfunction in a clinical setting. In addition, these technologies might result in safety problems that unintentionally hurt the patients. Post-marketing surveillance is crucial in resolving these problems because it aids in assessing the effectiveness of gadgets and concentrates on their safety. In addition to post-marketing surveillance, medical device harmonization is essential. The major objective of harmonization is to stimulate regulatory practice that is related to ensuring the quality, efficacy, performance, and safety of medical equipment. This will increase global demand and spur scientific innovation. Harmonization is an essential initiative that shortens the time needed for these medical products to be marketed and helps to lower the cost involved in doing so. In addition, it tries to improve the device's effectiveness and safety, restoring users' faith, and confidence in it.[3]

POST-MARKET MONITORING AND VIGILANCE

It is vitally necessary to continuously evaluate the safety and effectiveness of medical devices when they are in use since these qualities can only be demonstrated by seeing how a device performs under certain circumstances. No amount of thoroughness in the pre-marketing assessment process can foresee every potential incidence involving a misused equipment or device malfunction. Unexpected performance and safety issues can only emerge after real use.[4]

POST-MARKETING MONITORING TECHNIQUES

To assess the safety and dependability of MDs before they are marketed, a number of pre-market trials must be carried out, taking into consideration the possibility that after extensive use, serious safety concerns could surface due to an insufficient sample size or short follow-up period in the clinical trial. The discovery of the majority of MDs safety concerns is not significantly impacted by further pre-marketing clinical investigations in humans. Due to this, MD safety monitoring is a duty that necessitates systematic data collection and appropriate procedures for identifying security issues and communicating danger.[4]

Passive Observation

Passive monitoring refers to the ongoing observation of ARs brought on by the use of MDs. External parties, such as manufacturers, importers, healthcare providers, or even users or patients, report data to an institutional MD monitoring body, which then evaluates these incidents and risks of incidents to determine the appropriate course of action. Clear and stringent regulations for reporting occurrences have been implemented in some nations, whereas this is done voluntarily in others.[4]

Active Observation

There are two different types of active surveillance: One is based on post-clinical investigations performed either by a regulatory agency to verify compliance with crucial health and safety standards or by MD manufacturers as part of continuously supplying clinical evidence throughout their life cycle. These studies primarily focus on high-risk MD procedures like implants.

The other type consists of active MD registers that can produce information about the performance and safety of devices. "Prospective observational studies of subjects, with some common characteristics, that collect ongoing and supporting data over time on well-defined outcomes of

interest for analysis and reporting" are what registries are, according to WebMD. Registry data can reflect actual device performance and offer long-term findings for a broader population.[4]

INDIA'S MEDICAL DEVICE MARKET

In India, the Ministry of Health (MOH) and Family Welfare's Central Drug Standards Control Organization (CDSCO) is responsible for overseeing medical device regulation. The first steps toward establishing a dedicated MDs Division within the CDSCO were taken in 2004. Medical device guidelines were released on June 29, 2006. To regulate the manufacture of medical devices and to create high-quality medical devices, Schedule M III of the Drug and Cosmetic Rules guidelines was issued.

Classification of medical devices in India includes-

Class A (lowest danger levels),

Class B (low-to-moderate risk),

Class C (moderate-to-high risk), and

Class D (highest risk).[5]

The GHTF classification is the foundation for this categorization. Similar to the EU, India is moving toward implementing the ISO 13485:2003 QMS for Medical Devices and also contemplates third-party conformity evaluation by Notified Bodies. A valid wholesale license in Forms 20B and 21B, as well as an import license in Forms 8&9 from CDSCO, are necessary for the marketing of medical devices in India.

Before marketing, medical devices specified under the Notified Medical Devices and IVDs must register with the CDSCO.

A brief explanation of the registration procedure for medical devices in India is provided below:

A license is required to import, manufacture for sale or distribution, stock, exhibit, or offer for sale. The Central Licensing Authority (CLA) of India's CDSCO is in charge of all import devices licensing, as well as manufacturing, loan, and wholesale licenses for Class C and Class D medical devices.

State Licensing Authority (SLA) manages the manufacturing, loan, and wholesale licenses for Class A and Class B medical devices.[6]

CLASSIFICATION OF MEDICAL DEVICES

Table 1 illustrates the classification of medical devices in INDIA as per CDSCO.

REGISTRATION PROCESS OF MEDICAL DEVICES IN INDIA

Figure 1 illustrates the process flowchart for registration procedure of medical devices in INDIA as per CDSCO.

REPORTING OF MEDICAL DEVICES

Any adverse events (AE) related to medical devices may be reported using the Medical Device AE (MDAE) reporting form. This form includes an initial description, information on the AE that happened, and risks that the patient may face as a result. It is available for download from the IPC website. The Pharmacovigilance Program of India helpline number can also be used to report adverse occurrences. Patients and healthcare providers can properly report the MDAE form to SCTIMST or NCC.

Within 15 calendar days of an event's occurrence, CDSCO and the commission must be notified of any suspected major adverse effects. The MDAE form can be submitted immediately to the SCTIMST or the NCC after being filled out. Each report that is submitted to the commission is first divided into an initial, final, and follow-up report. Each report receives a special reference number. The commission requests more information from the patient or reporter before drawing a conclusion. Staff members with professional training who are present at the panel assess these reports to make sure the data are complete, reliable, and of the highest caliber. They are then submitted to the core technical committee for any necessary recommendations after being further examined by an outside subject expert group. The CDSCO is then notified of the suggestions for any subsequent regulatory action. It is sent to CDSCO, then on to the World Health Organization-Uppsala Monitoring Center, where it is entered in "vigiflow." The report is sent to the reporter or monitoring center with any pertinent remarks if it turns out that the data are lacking so that it can be completed and updated as necessary. The privacy of patients is rigorously protected at all times when studying and assessing case reports.[3]

MEDICAL DEVICE REGULATION IN CHINA

China's Health Authority, formerly known as the China Food and Drug Administration (CFDA), has been renamed to National Medical Product Administration (NMPA) in 2018. NMPA is China's government agency in charge of overseeing pharmaceuticals, cosmetics, and medical devices.[9]

The State food and drug administration (SFDA) must provide the company with pre-market approval before they may sell

Table 1: Medical device classification as per central drug standards control organization[7]

International Classification	Examples	Risk Level	Type of regulation
Class A	Thermometers, tongue depressors	Low	License not required but voluntarily applied to be licensed by SLA
Class B	Hypodermic needles, suction equipment	Low moderate	Approval by the SLAs
Class C	Lung ventilator, bone fixation	Moderate high	Approval by CLA
Class D	Heart valves, implantable devices	High	Approval by CLA

SLA: State licensing authorities, CLA: Central licensing authority

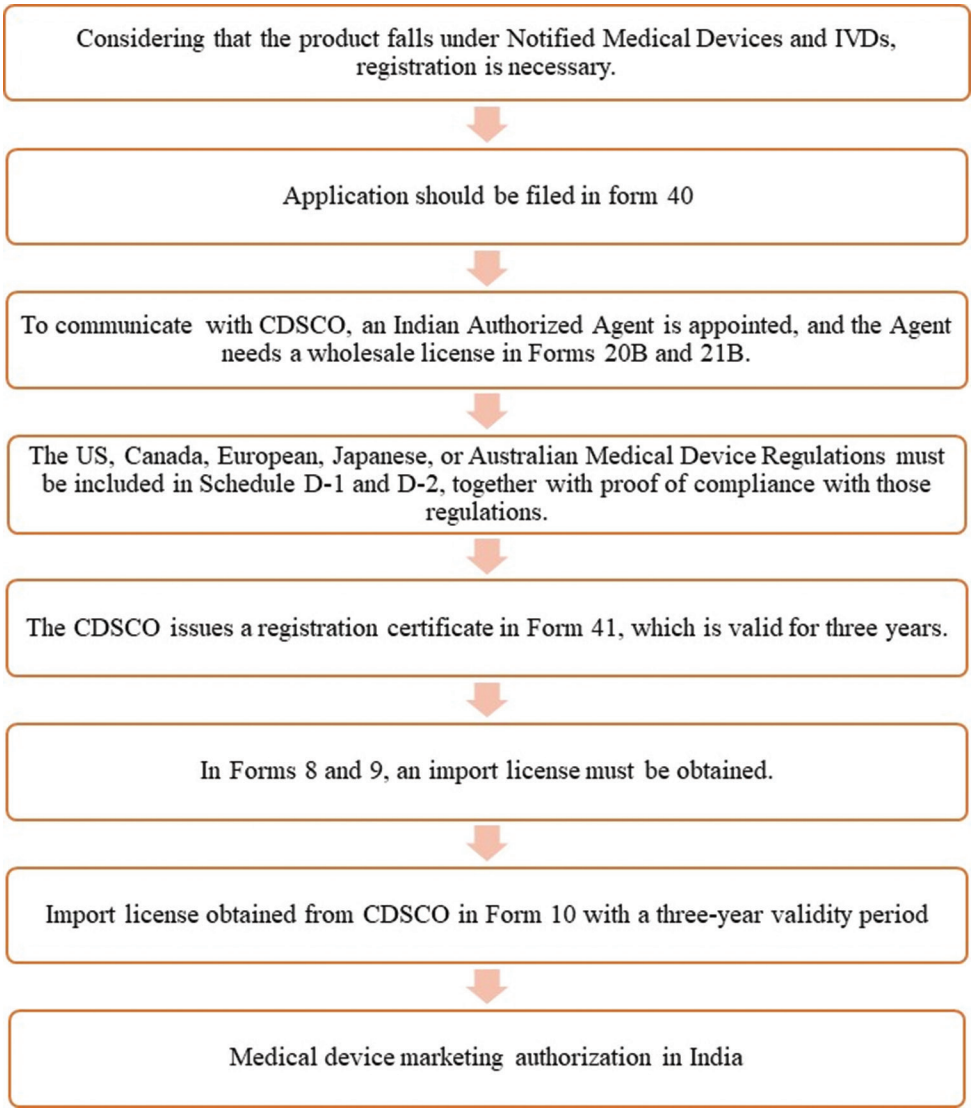

Figure 1: Registration process as per central drug standards control organization.[8]

their products in China. China should adhere to the following two rules:

1. The Medical Device Supervision and Administration Regulations of 2000
2. Administrative measures for the registration of medical devices (2004).[8]

CLASSIFICATION OF MEDICAL DEVICES

Medical devices in China are divided into three classifications, class I, class II, and class III, according to the risk associated with utilizing the device as per NMPA is stated in Table 2.

Table 2: Medical devices classification as per national medical product administration

Classification	Risk level	Examples
Class I	Medical Devices for which safe can be ensured through routine administration	Ear probes and scalpels
Class II	Medical Devices for which further control is required to ensure their safety of use.	Disposable umbilical cords
Class III	Medical devices that are implanted into the human body (or) use for life support,(or) pose potential risk to the human body and thus require strict safety surveillance.	Disposable venous infusion tubes and rubber plugs

The SFDA is directly in charge of managing all Class III and imported devices. In addition to medical device registration, some medical devices needed China Compulsory Certification (CCC).

The Chinese quality and quarantine officials (AQSIQ) manage the CCC mark.

Before a device may be sold on the market in China, it must be registered with the SFDA, which is now known as the CFDA.[8]

There are two rules that are observed in China

1. Measures for the management of medical device registration (2004) and
2. Regulation for the management and supervision of medical devices (2000).[8]

Previously, a medical device's registration was valid for 4 years. This is only required for Class-2 and Class-3 devices because they are thought to have higher dangers; it is now valid for up to 5 years.[3]

The NMPA of China has now expanded its pilot program for the registration of medical devices. This pilot initiative, which originally started in a free trade zone and now spans 21 provinces, was created to give the NMPA more practice using the registration system for medical equipment. The primary goal of this program is to build a Chinese market for cutting-edge medical devices.

By extending the use of the quality management system (QMS), the pilot project can improve the use of resources by enabling effective outsourcing. A medical device manufacturing company must therefore have operations in one of the provinces and possess some of the stated competences to be eligible to participate in a pilot project. Applicants must have full-time employees who have knowledge of post-marketing, regulatory bodies and affairs, and QMS, according to the NMPA. The employees should also be ready to assume responsibility for the security and caliber of medical equipment. The NMPA also demands the correct monitoring and tracing of the device lifetime (i.e., from research and development to materiovigilance).[3]

The company must first provide medical device samples to the NMPA for analysis if the medical device was not made in China. Class-2 and Class-3 devices must be submitted along with documentation proving that they have already received approval in the nation where they were produced. In addition, all device-related information, such as packing and labeling, needs to be translated into Mandarin. Finally, during the registration of Class-2 and Class-3 medical devices, all foreign producers are obliged to submit additional data from clinical studies. To register goods made outside of China, foreign manufacturers may additionally need an agent based in China.

The responsibilities of an agent include managing unfavorable events, regulating clinical studies, and offering technical services and maintenance support. Some medical equipment might also need CCC, in addition to registration. The Chinese quality and quarantine administration (AQSIQ), which oversees quality, monitoring, inspection, and quarantine, has control over the CCC mark.[3]

CHINA'S PROCEDURE FOR APPROVING MEDICAL DEVICES

Figure 2 illustrates the several steps needed to approve a medical device in China as per NMPA

REPORTING OF MEDICAL DEVICES

China's department of health conducts regional-level post-approval surveillance under the direction of the CFDA. One of its distinctive qualities is the way in which this surveillance program complements the central strategy.

Regulatory agencies and the health department will respond first when a medical device-related AE occurs. Although the MOH and CFDA are responsible for compiling reports of AEs and promptly reporting them to regulatory organizations. China's areas without temporary organizations have regional departments that carry out the same duties as the CFDA and MOH.

All regions and provinces' AE reports are gathered and analyzed by the CFDA's National Center for ADR Monitoring. Each region and each province have an ADR institution,

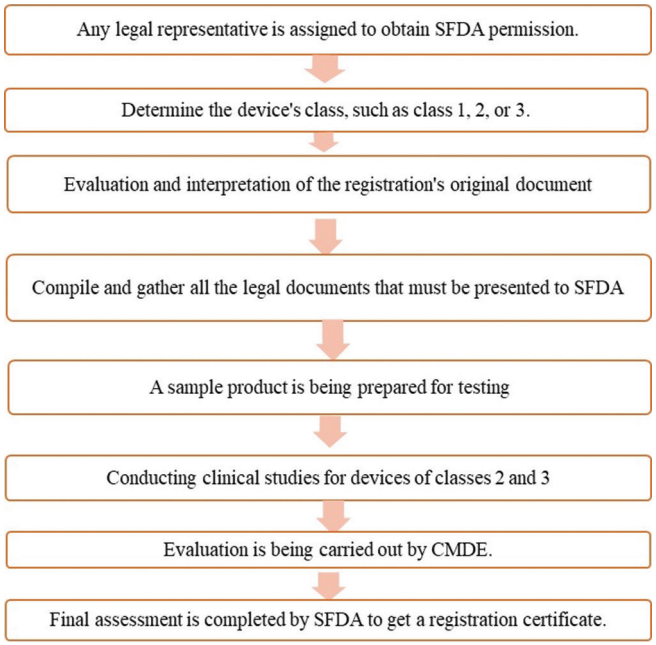

Figure 2: Approval process of medical devices in China[3]

which has better data access than the national ADR center but less analytical strength.

Local institutions of monitoring must receive injury reports within 15 days. As a result, these institutions are responsible for reporting.[3]

MEDICAL DEVICE REGULATION IN JAPAN

Japan's Ministry of Health, Labor, and Welfare (MHLW) is the regulatory body in charge of monitoring the nation's food and pharmaceutical industries as well as creating and implementing safety regulations for pharmaceuticals and medical devices. In cooperation with the MHLW, the Pharmaceutical and Medical Device Agency (PMDA) Organization is an independent organization that evaluates drug and medical device applications.

A federal legislation called the drugs Pharmaceuticals and Medical Devices Act (PMD Act) governs the production, marketing, and distribution of drugs and medical equipment. The current PMDA legislation in Japan are outlined in the PMD Act, also known as the Act on Securing Quality, Efficacy, and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics.[10]

CLASSIFICATION OF MEDICAL DEVICE IN JAPAN

Medical devices are classified into four classes as per PMDA in Japan which are stated in Table 3.

PREMARKET APPROVAL PROCESS IN JAPAN[10]

Premarket approval of devices in Japan is done by different regulatory body as per risk class of device which is stated in Table 4.

MEDICAL DEVICE REGULATIONS AND APPROVAL PROCEDURES IN JAPAN UNDER THE PMDA

Class I Device Regulations

The approval procedure for Class I Devices is known as Todokede.

Among the conditions for Class I medical device approval are the following: Category, name (generic/proprietary), intended use, shape, construction, and so forth.

The MAH has to file a notification to start the approval process, and the PMDA may not need to review this kind of medical device.

The QMS and the MHLW must be adhered to, as well as the PMD Act. On the other hand, manufacturing facilities need to be registered.[10]

Class II Device Regulations

The Ninsho approval process is utilized for Class II devices in terms of regulation. Class II medical device registration requires documentation that include information about the intended use, proprietary name, shape, structure, direction for use, manufacturing processes, storage conditions, and shelf life, among other things.

The MAH must begin the application process using a notarized body. PMDA and MHLW reviews may be required for some Class II devices.

The foreign producer might need a second level of authorization.

The maintenance of a QMS is also required for this kind of medical device.

The length of the process can range from 4 to 9 months, depending on the application's thoroughness and other factors.[10]

Class III and Class IV Device Regulation

Shonin (the approval process for Class III and Class IV devices) is the name given to the process by which Class III and Class IV devices are approved.

Table 3: Medical devices classification as per pharmaceutical and medical device agency[7,10]

International classification	Risk base medical device classification	Classification	Examples	Type of regulation
Class I (extremely low)	Devices with extremely low risk to the human body in case of problem	General Medical Device	X-ray films and *in vitro* devices.	Approval/certification not required (Notification/ self-declaration
Class II (low)	Devices with relatively low risk to the human body in case of problems	controlled Medical Device	Ultrasound devices and electronic endoscopes	Certification by third party certification
Class III (medium/high)	Devices with relatively high risk to the human body in case of problems	Specially Controlled Medical Device	Bone prothesis along with dialyzer	
Class IV (high)	Devices highly invasive to patients and with life-threatening risk in case of problem		Pacemakers and stent graft	Approval by the MHLW

Table 4: Medical devices premarket approval process as per PMDA

Class I	Class II (specified-controlled)	Class II-controlled)/ CLASS III/CLASS IV
Notification by PMDA	Certification by RCB	Approval by Ministry of Health, Labor, and Welfare
Application for product notification to PMDA	Application for product verification to RCB	Summary Technical Document to PMDA

PMDA: Pharmaceutical and medical device agency, RCB: Registered certified body

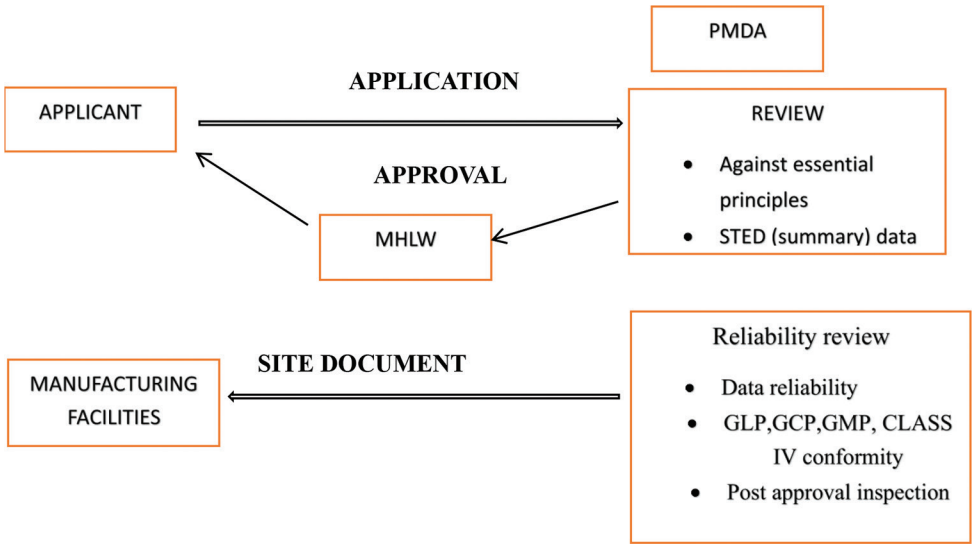

Figure 3: Approval process of medical devices in Japan[10]

With a few minor variations, the Class III and Class IV applications are substantially identical. This method also applies to medical equipment designated as Class II Controlled.

After receiving the application, the PMDA visits the production facility to do a QMS compliance assessment examination.

The application criteria include general requirements such as medical device category, intended use, efficacy risk analysis data, clinical data, and so on. The attachments include things like a summary of technical documentation (STED).

The class of the device and the type of approval process used determines how long it takes to approve an application.[10]

Table 5: Medical device guidelines comparison table

Parameters	India	China	Japan
Regulatory body	Central Drug Standards Control Organization	State Food and Drug Administration	Ministry of Health, Labor, and Welfare and Pharmaceutical and Medical Device Agency
Regulations	Schedule M III OF D&C ACT AND MDR 2017	1. Measures for the Management of Medical Device Registration (2004) and 2. Regulation for the Management and Supervision of Medical Devices (2000).	Pharmaceuticals and Medical Devices Act
Classification	Class A Class B Class C Class D	Class I Class II Class III	Class I Class II Class III Class IV
QMS requirement	ISO 13485 :2003	Chinese authorities have their own quality management system requirements for medical devices. However, these "GMP requirements" are very similar to ISO 13485	QS standard for medical devices
Assessment of technical data	Central Drug Standards Control Organization	National Medical Product Administration	PMDA, MLHW

Table 6: Meteriovigilance parameters comparison table

Parameters	India	China	Japan
Regulators for vigilance	Central Drug Standards Control Organization	China Food and Drug Administration	Ministry of Health, Labor and Welfare (MHLW)
Guidelines	Version 1.2 of the MvPI Guidance Document	National Medical Product Administration (NMPA)	Article 77-4-2 Enforcement Regulations of the Pharmaceutical Affair Law (translated by Jiho 2001, Inc. 2001) Section 64-5-2
Forms	Reporting Medical Device Adverse Event form	There is no particular medical device reporting form.	Reporting is completed by the Marketing Authorization Holder (MAH) and there is no special form.
Reporting timelines	Within 15 calendar days, all serious, life-threatening SUSAR instances must be reported. As soon as IPC, Ghaziabad finds the incident, a non-serious reporting must be completed within 30 calendar days.	Any case involving an injury must be submitted to a regional monitoring organization within 15 days.	Within 15 days of the adverse occurrence being recorded by the MAH, any death, major health injury, or unlisted case will be reported. The MAH will report any overseas death or serious case that has already been listed in 30 days.

MEDICAL DEVICE APPROVAL PROCESS IN JAPAN

Figure 3 illustrates approval process of medical devices in japan.

REPORTING OF AES OF MEDICAL DEVICES

The MAH immediately documents any unacceptable event that occurs in Japan. MAH then reports AE15, or an adverse drug event which resulted in the patient's death or any other major health injury, within 15 days. Any foreign death event or serious case that has already been listed and is marked as AE30 must be reported by the MAH within 30 days.[3]

MEDICAL DEVICE GUIDELINES COMPARISION

Table 5 illustrates the comparison of various parameters of medical devices in INDIA, CHINA, and JAPAN.

MATERIOVIGILANCE

Table 6 illustrates comparison of various materiovigilance parameters of medical devices in India, China, and Japan

CONCLUSION

Although China, India, and Japan have various laws governing medical devices, pre- and post-market procedures are however followed in these nations to ensure the marketing of high-quality product.

The CDSCO in India, which works under MOH and Family Welfare, the CLA, and the SLA, are responsible for granting licenses to import, produce for sale or conveyance, stock, display, or make available for purchase. SLA handles all aspects of Class A and Class B medical device assembling, lending, and wholesale licenses.

Japan is regarded as one of the most challenging markets for foreign manufacturers of medical devices due to its complicated enlisting process and linguistic barriers. The administrative body in charge of overseeing the nation's food and drugs, as well as developing and approving wellbeing standards for medical equipment and medications, is Japan's MHLW.

With regard to vigilance, medical equipments are subject to certain regulations. Reducing the risk connected to the use of medical devices is the aim of post-market surveillance.

By disclosing negative instances, important information that could stop similar future incidents is provided. Due to the variety and complexity of medical devices, a national incident reporting system must be developed and implemented immediately in every country as the standard protocol for reporting incidents to the authorities. Encouragement of event reporting is required to increase the effectiveness of the Medical Device Vigilance System.

A medical device needs to be monitored at every stage of its life cycle, including the pre-marketing phase (to acquire marketing permission) and the post-marketing phase (especially during the operational phase), to ensure its dependability and safety. The monitoring, quality control, and regulatory frameworks for MDs must be updated as quickly as the MDs are produced for the global market. The most certain assurance that this market will be mastered is the participation of all individuals (manufacturers, importers, regulators, healthcare providers, patients, and consumers).

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